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EXAMINER

SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 05/27/2003

19

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/836,439

Applicant(s)

Bizemont

Examiner

Richard Schnizer

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on Feb 24, 2003
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-39 is/are pending in the application.
- 4a) Of the above, claim(s) 13-16, 19, 22-29, and 31-38 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-12, 17, 18, 20, 21, 30, and 39 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on Apr 17, 2001 is/are a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some\* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\*See the attached detailed Office action for a list of the certified copies not received.

- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5, 11
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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### DETAILED ACTION

Information disclosure statements were received and entered on 11/28/01 and 3/27/02 and were entered as Paper Nos. 5 and 11, respectively.

An amendment was received and entered as Paper No. 18 on 2/24/03.

Applicant's election with traverse of group I drawn to methods of delivering an oligonucleotide for reversion of a K296E mutation in human RP1 *in vivo* to cells of an animal by iontophoresis is acknowledged. Traversal is on the grounds that search and examination of the entire application can be made without serious additional burden. This argument is unpersuasive because the various inventions are drawn to methods of treating different unrelated diseases with structurally and functionally distinct nucleic acids, as well as to creating animal model for a disease. Clearly, examination of these invention would require a non-overlapping search of unrelated material, causing an undue burden on the Examiner. Applicant further argues that none of the groups set forth in the requirement relate to a general method of transferring, *in vivo*, chimeric oligonucleotides into target cells of an animal or human tissue via iontophoresis as set forth in claim 1, because each group is specifically directed to one type of mutation. Applicant's attention is directed to page 9 of the restriction requirement issued 12/24/02 which states that claim 1 links inventions I-VI. Claim 1 will be examined as a generic claim. If claim 1 is found to be allowable, the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application.

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Group I as listed in the restriction requirement contains claims not drawn to an oligonucleotide for reversion of a K296E mutation. Specifically, claims 13 and 14 are drawn to oligonucleotides for reversion of a nonsense mutation caused by a C to A transversion at codon 347 of either a mouse or human cGMP-phosphodiesterase beta-subunit gene, and claims 15 and 16 are drawn to oligonucleotides that cause deletion, insertion or substitution of at least one nucleotide in a genomic sequence of a mouse or human HIF1alpha gene such that the encoded polypeptide is incapable of promoting hypoxia-induced neovascularization. As such, these claims were erroneously included in group I and will not be examined with the elected invention. Similarly, claims 19, 22-29, and 31-38 are withdrawn from consideration.

Claims 1-12, 17, 18, 20, 21, 30, and 39 are under consideration in this Office Action.

### *Drawings*

The drawings filed with the application are acceptable for examination purposes.

### *Claim Objections*

Claim 5 is objected to because it is ungrammatical. The word "modifying" should be substituted for the word "modified".

Claim 6 is objected to because "Cricks" is misspelled.

Claim 7 is objected to because the phrases "a chimeric oligonucleotide DNA/2'OMeRNA type" and "at least single mismatched oligonucleotide" are ungrammatical.

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Claim 10 is objected to because the phrase "partially responsible of an eye inherited pathology" is ungrammatical.

Claim 12 is objected to because "intraviteal" is misspelled.

Claim 20 is objected to because the phrase "electrically connection" in part (A) is ungrammatical. Claim 20 also lacks an article preceding the noun "bi-state switch" in part (H). Claim 20 also unnecessarily includes a comma between the words "flowing" and "between" in part (O).

Claim 30 is objected to because it contains non-elected subject matter, i.e. any oligonucleotide capable of reverting a mutation in the human RP1 protein sequence, an any oligonucleotide capable of reverting an R677-STOP mutation in human opsin.

Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

### ***Enablement***

Claims 1-12, 17, 18, 20, 21, 30, and 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

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enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In ex parte Forman, 230 USPQ 546 (bd. App. 1986) the board considered the issue of enablement in molecular biology and considered several factors. Consideration of these factors in the instant case follows.

*Nature of the Invention*

The claimed invention is drawn to methods for delivering into target cells of animal tissue in vivo by iontophoresis a chimeric oligonucleotide. The specification discusses chimeric oligonucleotides in the context of chimeraplasts, an art recognized term referring to an oligonucleotide comprising RNA and DNA. The chimeraplast, contains a sequence which is largely homologous to a target sequence in the host cell genome, and functions to recombine homologously with the target sequence, allowing the introduction of point mutations into the genome. This process is known as chimeraplasty. Unlike conventional antisense oligonucleotides, chimeraplasts have a characteristic self-complementary structure that allows them to exist in a largely duplex form. The invention is asserted to be useful to implement therapy, and to create in vivo disease models. The asserted novelty of the method in general is the use of iontophoresis to improve delivery of chimeraplasts to cells. The term "chimeric oligonucleotide" is a term of art embracing antisense oligonucleotides as well as chimeraplasts. However, the specification at page 2, lines 6-14 makes clear that by "chimeric oligonucleotide"

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Applicant intends chimeraplasts. For this reason, the scope of the term "chimeric oligonucleotide" was interpreted to be limited to chimeraplasts for the purpose of examination.

*Breadth of the Claims*

Claims 1-12, 20, and 21 are broadly drawn to methods of introducing a any chimeric oligonucleotide targeting any gene into an animal tissue in vivo. Claims 9-12 limit the site of delivery, but not the identity of the target gene. It is noted that claims 1-6, 9-11, 20, and 21 embrace any chimeric oligonucleotide, including conventional chimeric antisense oligonucleotides, and are not limited to those having a typical duplex chimeraplast structure. Claims 17 and 18 further limit claim 1 to the use of an oligonucleotide complementary to a human RP1 gene, with claim 8 specifying the elected species of an oligonucleotide capable of reverting a K296E mutation. Claims 30 and 39 are drawn to specific oligonucleotides which must be capable of reverting a K296E mutation in the human opsin gene. The claims also embrace methods of therapy based on the deliver of chimeric oligonucleotides. This is clear in view of the specification at page 1, lines 12-14 which states that the invention relates to a gene therapy method of treating human eye diseases, and in view of claim 39 which requires that a composition comprising a chimeric oligonucleotide must be enabled for pharmaceutical use.

*State of the Art, Predictability of the Art, and Level of Skill of Those in the Art.*

As an initial matter, it is noted that claims 1-6, 9-11, 20, and 21 embrace methods of delivering any chimeric oligonucleotide, including conventional chimeric antisense oligonucleotides, and are not limited to those oligonucleotides having a typical duplex

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chimeraplast structure. These claims are enabled to the extent that they are rendered obvious by the prior art. A thorough reading of the specification reveals that the disclosed invention is intended to be a method of delivering chimeraplasts, the breadth of claims 1-6, 9-11, 20, and 21 notwithstanding. As such, the enablement rejection focuses on the invention as it is intended to be used in light of the specification, i.e. as a method of delivering chimeraplasts in vivo.

The state of the art of chimeraplasty at the time of the invention is set forth by van der Steege et al (Nature Biotechnology 19: 305-306, 4/2001), van der Steege indicates that very few laboratories were able to obtain perceived success using chimeraplasts at the time of the invention. The laboratory of van der Steege, as well as others, persistently failed to reproduce results of another possibly successful laboratory. See e.g. lines 1-10 of paragraph bridging pages 305 and 306. Further, despite obtaining a small degree of apparent success upon visiting this laboratory, van der Steege was subsequently unable to reproduce this result in his own laboratory. Although the prior art comprises scattered examples of apparent success using chimeraplasty, these results were viewed with skepticism prior to and at the time of the invention. Thomas and Capecchi (Science 275(5305): 1404-1405, 1997) noted that one published study indicating a 50-80% mutation rate lacked the proper controls. Stasiak et al (Science 277(5325): 460-462, 1997) concurred with Thomas and Capecchi, and indicated that such results were likely false positives due to artifact or experimental error. Zhang et al (Antisense & Nucl. Acid Drug Dev. 8: 531-536, 1998) attempted to alter nucleic acid sequences using each of 42 different chimeraplast constructs and six different delivery methods, and attempted to perform experiments as closely as possible to

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those previously published. However, Zhang et al did not achieve a single positive result. Several explanations were posited, including the possibility that the selected target sites were inaccessible, and the possibility that successful application of the method may be limited by unpredictable factors such as chromatin structure, i.e. histone content or position (see abstract and page 535, column 2, lines 1-18 of last paragraph). Notably, Zhang et al concluded that perceived positive results in the prior art may have been due to PCR artifacts (see paragraph bridging columns 1 and 2 on page 535). Thus at the time of filing, the legitimacy of using chimeraplasts to modify nucleic acid sequences was in doubt, and it was clear that any apparent positive results obtained at that time were not routinely reproducible by those having a high level of skill in the biotechnological art. This is clear evidence of a high level of unpredictability in the art at the time of the invention.

Subsequent to the time of the invention Alberque-Silva et al (Nature Biotechnology 19: 1011, 11/2001) attempted to use chimeraplasty in a variety of experiments, but failed to achieve any significant positive result above background level. Alberque-Silva set forth four criteria for establishing whether or not apparent positive chimeraplasty results are significant, (see four bullets in column 1). Notably, Alberque-Silva indicates that of "the 20 original studies published on chromosomal gene conversion using [chimeraplasty], we found none fulfilling all four of our criteria."

The concerns of Thomas and Capecchi, Stasiak, Zhang, and Alberque-Silva appear to have been well founded in view of a recent review of chimeraplasty (See "The Strange Case of Chimeraplasty, Science (2002) 298:2116-2120). This article indicates that while 9 different

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laboratories have published apparently successful chimeraplasty studies (see page 2119, column 1, lines 8-12), these results are viewed with skepticism by those of skill in the art, particularly because of the large number of laboratories that have failed to reproduce these results. "*Science* spoke to researchers from over 30 laboratories that had tried [chimeraplasty] and failed to produce evidence that they could target and correct dysfunctional genes, either in vitro or in vivo. Researchers at biotech companies such as Epoch Biosciences, Isis pharmaceuticals, Millennium Pharmaceuticals, and Lexicon Genetics all failed to get chimeraplasty to work in their labs. Experienced gene-targeting researchers at MIT's Whitehead Institute, NIH..., Maine's Jackson Laboratory, and Sweden's Karolinska Institute also saw no effects." (see paragraph bridging columns 1 and 2 on page 2120). "The great majority of researchers interviewed by *Science* say they find the negative results, even though unpublished, more persuasive than the positive ones because they come from independent labs with considerably more experience in gene repair and gene therapy than those that succeeded have." This sentiment is embodied in a quote from Neal Copeland, director of the Mammalian Genetics Laboratory at the National Cancer Institute who said "[t]he people I trusted, the ones who are really good, invested a lot of time, and none of them got it to work." From this it is clear that even those of the highest level of skill in the biotechnological art could not perform chimeraplasty with routine success, and that at best, it must be viewed as a highly unpredictable art. It is important to note that many of these unsuccessful experiments were carried out in vitro using a variety of delivery techniques such as cationic lipid transfection, electroporation, and microinjection, that have proven effective for the

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delivery of oligonucleotides to cells (See e.g. Zhang (1998), abstract). So, it is highly unlikely that poor oligonucleotide delivery explains the failure of these experiments, and it is equally unlikely that the use of iontophoresis as a delivery technique, as instantly claimed, would have improved the outcome of these experiments.

*Guidance and Examples in the Specification*

The specification provides no new guidance with respect to the general structural characteristics of chimeraplasts, and the asserted novelty of the invention lies in the use of iontophoresis to enhance delivery of the oligonucleotides. See e.g. page 6, lines 5-9 of the specification.

The specification teaches a single working example of iontophoresis-mediated chimeraplasty at pages 25-26. A single chimeric oligonucleotide designed to correct a mutation in beta phosphodiesterase was delivered to mouse retinas in vivo by iontophoresis or by subretinal injection. Gene conversion was measured by restriction digest of RT-PCR products. Digestion with BsaI was consistent with gene conversion. Digestion with DdeI was consistent with no conversion. The specification asserts that the results are consistent with gene conversion, however the results appear to be inconclusive for a number of reasons. First, BsaI appeared to digest the control DNA not injected with the mutagenic chimeraplast. See lanes 17 and 18. Applicant explains this lack of specificity as already observed in control lane 5. However, if this explanation is accurate, then it is unclear how significant results can be obtained if the restriction enzyme used shows non-specific behavior. Secondly, the prior art and post-filing art teach that PCR-based

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assays of chimeraplast-driven gene conversion are prone to artifactual results. See Zhang (1998) and Alberque-Silva (2001) above. It is noted that the specification discloses a "highly significant increase in rod-photoreceptor survival" only in chimeraplast/iontophoresis-treated animals, as determined in cell counting assays. However, the results on which this conclusion are based are not presented so an evaluation of the data is not possible. Even if the working example in the specification is significant, and there is substantial reason to doubt that it is, the specification fails to enable the invention as claimed. The prior art teaches that many of those of the highest skill in the art were unable to obtain success with gene conversion even in vitro where it was clear that the oligonucleotides could enter cells. Moreover, those who obtained apparent success with chimeraplasty by performing it in laboratories that had published successful experiments were unable to reproduce this success upon returning to their own laboratories. See above. The specification has failed to teach how to use the invention to perform gene conversion reproducibly with the unlimited array of chimeraplasts embraced by the broad claims, and it does not present any working example using the chimeraplast recited in the narrowest elected claims, i.e. SEQ ID NO:3. The specification fails to teach what structural chimeraplast features, or technical method steps, will ensure one of skill in the art of achieving reproducible, routine success in the practice of the invention. This is a critical failure in view of the extremely unpredictable state of the art.

It is important to note that although chimeraplasty has been highly unpredictable in terms of reproducibility, the prior art does not identify poor oligonucleotide delivery as an explanation for this problem. Furthermore, it is not clear that iontophoresis results in better delivery of

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chimeraplasts than do cationic lipid transfection, electroporation, or microinjection. It follows that one of skill in the art would not reasonably expect to improve the predictability of chimeraplasty through the use of iontophoresis as a delivery technique.

*Amount of Experimentation Required to Practice the Invention*

In view of the uncertain state of the art at the time of the invention, the high level of unpredictability associated with chimeraplasty, the persistent and routine failure of those of skill in the art to obtain positive results using chimeraplasty or to reproduce apparently positive results published in the art, and the failure of the specification to provide substantial additional guidance to that available to those of skill in the art at the time of the invention, one of skill in the art would have had to perform undue experimentation in order to use the invention as intended to effect gene conversion with the broad range of oligonucleotides and in the broad range of tissues contemplated.

Even if Applicant is able to overcome this rejection, the following enablement problems remain.

1. The elected invention requires an oligonucleotide capable of reverting a K296E mutation in human RP1. The restriction requirement that set forth this group was based on the information in the specification and claims as filed. See e.g. the specification at page 7, lines 17 and 18, and at page 13, lines 9-16. However, wild type human RP1 does not comprise a lysine residue at position 296, instead it contains a proline residue at this position. See e.g. Fig. 1b on page 256 of Sullivan et al (Nature Genetics (1999) 22(3): 255-259). In fact the K296E mutation occurs in

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opsin/rhodopsin, not in RP1. RP1 and opsin/rhodopsin are distinct polypeptides encoded by distinct genes. See e.g. Sullivan et al (1999) who report the sequence of RP1, and Nathans et al (Proc. Nat. Acad. Sci. (1984) 81(15): 4851-4855) who report the sequence of opsin/rhodopsin. Therefore there is no such thing as a K296E mutation of human RP1, and one of skill in the art could not make an oligonucleotide capable of reverting such a mutation.

2. In one embodiment, Claim 2 requires transferring "said chimeric oligonucleotide" into patient tissue by iontophoresis prior to applying the chimeric oligonucleotide to, or injecting the chimeric oligonucleotide into, the patient. The specification and the prior art fail to teach how to transfer an oligonucleotide into tissue by iontophoresis prior to actually contacting the tissue with the oligonucleotide. This would appear to be a physical impossibility, and one of skill in the art could not practice this embodiment without undue experimentation.
3. Claim 5 embraces chimeric oligonucleotides that modify proteins, i.e. by direct interaction with the proteins. The specification and the prior art fail to teach any example of any chimeric oligonucleotide that modifies proteins by direct interaction with the protein rather than by interaction with the gene encoding the protein. One of skill in the art would have to perform undue experimentation in order to develop this technology which does not appear to exist.
4. Claims 1-5, 9, 10, 20, and 21 embrace methods of delivering non-mutagenic chimeraplast oligonucleotides, i.e. chimeraplast oligonucleotides that contain no mismatch with the target sequence. However, the specification fails to teach how to use a non-mutagenic chimeraplast oligonucleotide. The prior art reveals no use for such a method and none is readily apparent, so

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one of skill in the art would have to perform undue experimentation in order to use a method to deliver non-mutagenic chimeraplasts.

5. Claim 20 part (K) requires that the donor electrode must be both a needle and a pad electrode. Neither the specification nor the prior art of record teaches such an electrode. US Patent 6,001,088, on which the specification depends for description of this embodiment, teaches that needle and pad electrodes are alternative forms of electrodes, and it does not disclose a combination needle and pad electrode. Therefore in order to practice the invention as claimed, one of skill in the art would have to invent a combination needle and pad electrode. Such experimentation is undue.

### *Written Description*

Claims 1-12, 17, 18, 20, and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As generic claims, claims 1-7, 9, 20, and 21 comprises the genres set forth in claims 8 and 10-12. In order for claims 1-7, 9, 20, and 21 to supported by an adequate written description, claims 8 and 10-12 must be so supported.

Practice of the methods of claims 8, 11, and 12 requires knowledge of the genus of sequences of mutated genes that are responsible for any inherited pathology.

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Practice of the method of claim 10 requires knowledge of the genus of genes that, when mutated, are at least partially responsible for an eye inherited pathology.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species has been described by complete structure, such as nucleotide sequence, next it is determined whether a representative number of species has been described by other relevant identifying characteristic. Applicant is referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at [www.uspto.gov](http://www.uspto.gov)). The following passage is particularly relevant.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

The instant specification discloses chimeric oligonucleotides designed to revert mutations in cGMP phosphodiesterase beta subunit, RP1, opsin, and HIF1alpha. Clearly the genus of mutated genes responsible for an inherited pathology is larger than this group. Even the narrower genus of genes that can be partly responsible for an inherited eye pathology is substantially wider than this group,. For example Graeme et al (2002) taught an expressed sequence tag library of

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adult human lens, and found over 2000 non-redundant transcripts, any of which could conceivably be linked to a heritable disease. The specification describes none of these sequences, nor does it describe by relevant identifying characteristics, i.e. by functional characteristics coupled with a known or disclosed correlation between structure and function, any genes other than cGMP phosphodiesterase beta subunit, RP1, opsin, and HIF1alpha. Further, the specification fails to teach what, if any, combination of structural and functional characteristics these genes have in common that makes them members of the recited genus. As such, the specification fails to describe a representative number of species of a very broad and diverse genres, and one of skill in the art could not conclude that applicant was in possession of these genres at the time of the invention.

In viewing the invention in terms of the elected species requiring an oligonucleotide that reverts a K296E mutation in human RP1, the claims also lack adequate written description. Because the K296E RP1 mutation does not exist for the reasons given above under enablement, one of skill in the art could not conclude that Applicant was in possession of an oligonucleotide capable of causing reversion of the mutation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 1-12, 17, 18, 20, 21, 30, and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and dependents are indefinite because they draw a distinction between humans and animals, depicting them as alternatives. Humans are members of the kingdom of Animalia, and are by definition animals, so the claims are unclear. Deletion of "or human" is suggested. Alternatively the words "a non-human" could be substituted for the word "an" immediately preceding the word "animal".

Claim 1 and dependents are indefinite because they recite "the patient tissue" without proper antecedent basis. Substitution of "animal" for patient is suggested.

Claim 2 is indefinite because it fails to further limit claim 1. Claim 1 places no limitation on when step b is performed relative to step a, so step b may be carried out before, during or after step a. Claim 2 simply states explicitly what is implicit in claim 1, i.e. that step b carried out before, during or after step a. This does not further limit claim 1.

Claim 4 is indefinite because it recites the term "specifically", which is a relative term. The term "specifically" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Specifically, the parameter of "hybridizing" is rendered indefinite by the use of the term "specifically".

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Claims 7, 8, 11, 12, 30, and 39 are indefinite because they recite the phrase "chimeric oligonucleotide DNA/2'OMeRNA type", and or the phrase chimeric oligonucleotide DNA/2'OMeRNA, and/or the phrase "DNA/2'OMeRNA". These phrases are jargon and are not given a limiting definition in the specification, so one of skill in the art cannot know the metes and bounds of the claims. It is suggested that the claims should recite instead a "chimeric oligonucleotide comprising DNA and 2' methoxy RNA".

Claims 7, 8, 11, 12, 30, and 39 are indefinite because the required organization of the chimeric oligonucleotide is unclear. More specifically, it is unclear as to whether the claims require that the methoxy RNA must flank the polynucleotide hairpin loops and G-C clamp, or whether it must flank only the stretch of DNA. These claims are also indefinite because the metes and bounds of "a stretch" of DNA are unclear. How many bases constitute a stretch? How can one determine what are the metes and bounds of the protection desired by Applicant?

Claim 8 is indefinite because it is unclear which DNA/RNA sequence is referred to by "that DNA/RNA sequence." The oligonucleotide of claim 7 has at least two, if not four, distinct DNA/RNA junctions, so the phrase "that DNA/RNA sequence" could refer to any one of them.

Claim 8 is also indefinite because there is no clear antecedent basis for "that mutation which is desired to be reverted". The claim would be clearer if it were drawn to "[t]he method of claim 7... wherein part of the chimeric sequence is complementary to part of sequence of genomic DNA comprising a disease-causing mutation, wherein the chimeric oligonucleotide is not complementary to the mutation itself, but only to sequences immediately 5' and 3' of the mutation,

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and wherein these complementary regions of the oligonucleotide flank a nucleotide or nucleotides intended to revert the disease-causing mutation." It is noted that such an amendment would not overcome the written description and enablement rejections set forth above.

Claim 10 is indefinite because it is unclear whether applicant intends to claim "epidermal and dermal tissue" as a single species of the Markush group, or if epidermal is intended to be separate species from dermal. If they are intended to be separate species, then the word "tissue" should be inserted after "epidermal". If they are intended to be a single species, then the word "and", immediately before "dermal", should be deleted and reinserted immediately before "epidermal".

Claims 20 and 21 are indefinite because they recite "the iontophoresis system used in step b)" without antecedent basis.

Claim 20 is indefinite because it recites "the chemical species without antecedent basis" in part (B).

Claim 20 is indefinite because it recites "said electrode", "said iontotherapeutic delivery", "the electrode", "said ionized pharmaceutical", and "said membrane" without proper antecedent basis in part (G).

Claim 20 is indefinite because it recites "the effects" without antecedent basis in part (L).

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*Conclusion*

No claim is allowed. Claims 7, 8, 11, 12, 17, 18, 30, and 39 are free of the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

  
DAVE T. NGUYEN  
PRIMARY EXAMINER

Richard Schnizer, Ph.D.